techniques such as DTI to delineate tumour volume. <5% patients develop disease recurrence predominantly in the low-dose radiotherapy (<30 Gy) region. Identification and prediction of dosimetrically distinct patterns of treatment-failure that can be correlated with specific molecular profiles may be useful to individualize and thereby, improve survival of glioblastoma.

Reference:1. Stupp R, Hegi ME, Mason WP et al. Lancet Oncol. 2009; 10:459

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Malignant mucosal melanoma in the upper aerodigestive tract treated with carbon ion RT at CNAO: preliminary results

V. Vitolo[1], P. Fossati[1], M. Bonora[1], A. Iannalfi[1], M.R. Fiore[1], V. Vischioni[1], E. Ciurlia[1], S. Ronchi[1], S. Molinelli[2], A. Mirandola[2], E. Gallio[2], S. Russo[2], D. Panizza[2], M. Ciocca[2], M. Krengli[3], F. Valvo[1], R. Orecchia[4]

[1]*Centro Nazionale di Adroterapia Oncologica, Area Clinica, Pavia, Italy*

[2]*Centro Nazionale di Adroterapia Oncologica, Fisica Medica, Pavia, Italy*

[3]*Azienda Ospedariero - Universitaria Maggiore della Carità di Novara, Radioterapia, Novara, Italy*

[4]*Istituto Europeo di Oncologia, Radioterapia, Milano, Italy*

Purpose/Objective: Analyze the toxicity of and response to carbon ion radiotherapy (CIRT) in patients diagnosed with malignant mucosal melanoma (MMM) in the upper aerodigestive tract of the head and neck area inoperable, with macroscopic residual/relapse after surgery or in patients that refused surgery.

Materials and Methods: We analyzed data coming from patients with an MMM diagnosis in the head and neck area treated at CNAO from May 2013 to October 2014 with carbon ion radiotherapy at a total dose of 68,8 GyE in 16 fractions. The toxicity was evaluated in the scale CTCAE v.4.0 and the response to the disease with MRI every three months from CIRT.

Results: We treated 8 patients (average age 72 years-old, range from 48 to 86) with MMM in the following areas: nasopharynx (1 patient), lacrimal duct (1 patient), nasal cavity (4 patients), mouth (1 patient), oropharynx (1 patient). 3 patients were treated with macroscopic residual after surgery, 2 patients after post-surgical relapse with positive margins, 3 patients only with CIRT. Average GVT was 31.47 cc (range 7.76-84.23 cc). 2 patients received systemic therapy pre-CIRT (1 out of 2 also post-CIRT). In the course of treatment, toxicity appeared acceptable (≤ G2 in 7 patients, G3 mucositis in 1 patient). The mean follow-up was 8 months (range 3-12). 3 months follow-up was available for 5 patients (1 patient completed CIRT one month ago, 2 patients died at 2 and 3 months after CIRT for the progression of distant disease) and showed low grade acute toxicity (G0 in 4 patients, G1 in 1 patient); at 3 months response evaluated with RECIST was CR in 2 patients and PR in 3 patients. Follow-up at the 6 months (available for 4 patients) confirmed low intermediate toxicity (G1 in all the patients), partial response (PR) in 3 patients and complete response (CR) in 1 patient. Follow-up at 9 months was available for 4 patients, the highest toxicity was G2 in 1 patients, PR in 1 patient and CR in 3 patients. Follow-up at 12 months was available only for 1 patient, with confirmed CR and toxicity G1. Progression disease took place in 2 patients, respectively at 0 and 1 months after CIRT (in both cases distant PD in absence of local PD).

Conclusions: Recommended treatment for patients with MMM in the head and neck area is surgery followed by adjuvant radiotherapy. In the event of macroscopic residual or not resectable disease, preliminary results observed at CNAO confirm that CIRT guarantee good local control, allowing high dose on complex volume and in the proximity of critical organs with very low

These data are preliminary; larger patient number and longer follow up are needed.

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Efficacy of combination treatments of a NOTCH inhibitor and chemoradiotherapy in an orthotopic glioma model

S. Yahyanejad[1], P.V. Granton[2], S. Van Hoof[2], L. Barbeau[1], J. Theys[1], F. Verhaegen[2], M. Vooijs[1]

[1]*GROW - School for Oncology and Development, Radiation oncology (Maastro Lab), Maastricht, The Netherlands*

[2]*GROW - School for Oncology and Development, Maastro Clinic, Maastricht, The Netherlands*

Purpose/Objective: Glioblastoma multiforme (GBM) is the most common and malignant brain tumor in adults. Aggressive multimodal treatment using surgery followed by radiotherapy and chemotherapy extends the median survival of GBM patients to approximately one year after diagnosis. Treatment is not curative because of the intrinsic and acquired radiation resistance of a subpopulation of tumor cells. Notch inhibition has been shown to impair the tumorigenic capacity of these cells as well as enhance their sensitivity towards radiation. Therefore, we investigated if a highly potent and clinically approved Notch pathway inhibitor improves tumor control when combined with radiotherapy and chemotherapy in an orthotopic GBM mouse model.

Materials and Methods: To investigate combinations between standard of care treatment and Notch inhibitors, we used a three dimensional spheroid assay from commercially available and primary glioma cell lines in which spheroid volume growth delay can be quantitatively monitored in individual spheroids. In addition, we assessed the expression of the putative glioma stem cell marker CD133 performing flow cytometry. Furthermore, therapeutic efficacy was evaluated in an orthotopic glioma tumor model wherein tumor progression was evaluated using bioluminescence (BLI) and contrast-enhanced micro-computed tomography (CT) imaging and confirmed using histopathological analysis. Dedicated small animal treatment planning software (SmART-Plan) was used to create irradiation plans to deliver a conformal dose of 8Gy to the tumor with minimal normal tissue exposure. A small animal precision irradiation platform (PXI, XRAD 225Cx, CT, USA) was used for micro-CT imaging and radiation delivery.

Results: Notch blockade alone did not affect the sphere volume compared to control, whereas combination treatment with radiation resulted in a substantial spheroid growth delay ($p=0.004$). Radiation treatment enhanced the expression of the stem cell marker CD133, while Notch blockade reduced CD133 expression. We found a strong correlation between CT and BLI imaging of tumor growth in vivo (Pearson coefficient $(r)=0.85$, $p=0.001$). The potential of Notch inhibition